UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,772	11/09/2001	Robert L. Stout	31645	7479

7590 04/16/2004

HOVEY, WILLIAMS, TIMMONS & COLLINS
SUITE 400
2405 GRAND BLVD.
KANSAS CITY, MO 64108

EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/037,772	STOUT ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *11 and 25-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/20 and 2/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Please note that the correct Art Unit location of your application under prosecution at the USPTO is 1651, not 1743 as recited in the Response to Restriction Requirement filed January 14, 2004. To aid in correlating any papers for this application, please ensure that all further correspondence regarding this application should be directed to Art Unit 1651.

2. The assigned Examiner to your application in the USPTO is Dr. Kailash C. Srivastava. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Kailash C. Srivastava in Art Unit 1651.

Claims Status

3. Claims 1-51 are pending.

Restriction/Election

4. In accordance with applicants' amendment filed January 14, 2004 and newly added Claim 51, the restriction requirement in Office action mailed September 15, 2003 is hereby revised as follows:

- Group I, consisting of claims 1-10 and 12-24 drawn to a method to screen a drug (i.e., a chemical compound, wherein said compound modifies the activity of an enzyme on a given substrate), classified under Class 435, subclass 7.71, for example.

- Group II, consisting of claim 11 drawn to a method to assay an enzyme, classified under Class 435, subclass 4, for example.

- Group III, consisting of claims 25-37 and 41-51 drawn to a method to screen a β-blocker drug by determining receptor-ligand binding, classified under Class 435, subclass 7.1, for example.

- Group IV, consisting of claims 38-40 and 51 drawn to an assay to screen an ACE-inhibitor drug or metabolite thereof (i.e., a chemical compound, wherein said compound modifies the activity of an enzyme on a given substrate), classified under Class 435, subclass 7.71, for example.

5. Applicant's election with traverse of Group I, Claims 1-10 and 12-24 filed January 14, 2004 to election requirement in Office Action mailed September 15, 2003 is acknowledged and entered. Applicants' traversal is on the grounds that claims in Groups III and IV and newly added Claim 51 should be examined together with claims encompassing the invention in Group I because "all Claims relate to determining the presence and/or activity levels of drugs in fluid samples using an assay capable of such a determination".

Applicant's arguments have been carefully considered, but are not found persuasive because of the reasons of record on pages 2-3 in Office Action mailed September 15, 2003 and for the reasons stated below: as applicants themselves assert on page 12, Lines 8-12 of the reply cited *supra*; claims encompassed in each of the groups I and III-IV have been drawn to three different inventive methods, wherein each method is based on a different concept and involves different assay steps, i.e., invention of Group I, is drawn to an enzyme assay; whereas those encompassed in invention for Group III utilize a ligand binding and invention in Group IV is a "forensic assay" that is not limited to either an enzyme or ligand-receptor binding assay.

Contrary to applicants' assertion, newly added Claim 51 does not encompass invention in Group I, because said invention is drawn to a method to assay only for a drug, not "metabolite thereof" via assaying the activity of an enzyme on a given substrate. Only Group IV invention is drawn to "active drug or an active metabolite thereof". Thus, inventions outlined in each of the Groups I, III and IV do not share the same steps and are not connected to each other in design, operation and/ or effect. Furthermore, a restriction requirement is made among/between inventions not claims. In addition, the search for each of the distinct inventions of Groups I and III-IV is not co-extensive particularly with regard to the literature search. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the condition for patentability is different in each case. Thus, it will be an undue burden to examine all of the inventive Groups in one application. Therefore, the restriction requirement is still deemed proper and is made FINAL.

Accordingly, Claims 11 and 25-51 are withdrawn from further consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Examiner suggests that to expedite prosecution, the non-elected claims cited above be canceled in response to this Office action.

6. Claims 1-10 and 12-24 are examined on merits.

Information Disclosure Statement

7. Applicants' Information Disclosure (i.e., IDS) filed February 20, 2004 and Supplemental Information Disclosure filed February 23, 2004 have been made of record and considered.

Claim Rejections - 35 U.S.C. § 112

8. Following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 1-10 and 12-24 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 1 is incomplete because it lacks reference to a standard activity. Examiner suggests that Claims 1 and 2 be combined to overcome this discrepancy in Claim 1.

- Claims 13-14, 20-22 and 24 lack antecedent basis because these claims depend from Claim 12 that encompasses qualitative measurement of just determining an ACE inhibitor. However, Claims 13-14, 20-22 and 24 encompass quantitative measurements.

Claim Rejections – 35 U.S.C. § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-9 are rejected under 35 U.S.C. §102(b) as anticipated by Fobare et al. (U.S. Patent 4,792,614).

Fobare et al. teach a method to determine a drug in a fluid sample, wherein said drug inhibits the activity of the enzyme 3-Hydroxy-3mrthylglutaryl-COA reductase (i.e., HMG-COA reductase). The method comprises measuring at 37° C, the activity of HMG-COA reductase in presence and absence of said test compounds and is measured as the radioactivity of the 14C mevalonolactone produced as a result of reduction of 14C HMG-CoA (Column 9, Lines 50 to

Column 10, Line 33). Thus, Fobare et al. teach a method to determine a drug that inhibits the activity of an enzyme in a fluid sample. Fobare et al. also measure HMG-COA reductase activity in absence of said drug compounds and evaluate the inhibition of HMG-COA reductase by said drug relative to HMG-CoA reductase activity in absence of said drug. Fobare et al. also assayed HMG-CoA reductase activity in presence of varying concentrations of said test drug. Thus Fobare et al., teach determining the presence of a drug in a fluid sample via measuring the inhibition in the activity of a given enzyme on a given substrate by said drug. Since said inhibition in enzyme activity is measured with varying concentration of test drugs, Fobare et al also teach that a decrease or increase in the enzyme activity level is a function of increasing drug concentration in said fluid, i.e., at low concentration of drug, the enzyme activity is increased relative to the inhibition of enzyme activity at higher drug concentration.

Therefore, the reference anticipates the claims.

12. Claims 1-10, 12-18 and 20-23 are rejected under 35 U.S.C. §102(b) as anticipated by Yoshikawa et al. (U.S. Patent 5,369,015).

Yoshikawa et al. teach measuring ACE inhibition by a variety of inhibitors obtained from a variety of sea foods (Column 3, Line 40 to Column 6, Line 54). ACE inhibition was evaluated via measuring the absorbance of reaction mixture at an O.D. of 228 nm. Said activity was measured in absence and in presence of said inhibitors (Column3, Line 67 to Column 4, Line 28) and expressed as IC_{50} (μg/ml) with the OD_{228} value in the absence of inhibitor being taken as 100% ACE activity. Yoshikawa et al. express the ACE inhibition as IC_{50} (μg/ml) with the OD_{228} value, therefore, they have inherently measured the ACE activity with increasing and decreasing concentrations of inhibitors, compared activity levels with a standard curve and inherently also

measured the decrease in the level of enzyme activity with increase in the concentration of test inhibitor. Thus, Yoshikawa et al. teach measuring the presence of a drug in more than two fluid samples and comparing the activity of ACE in presence of a variety of ACE inhibitors with the ACE activity in absence of said inhibitors.

Therefore, the reference anticipates the claims.

13. Claims 1-10, 12-18 and 20-22 are rejected under 35 U.S.C. §102(b) as anticipated by Brunner et al. (U.S. Patent 5,407,803).

Brunner et al. teach measuring ACE activity in blood/plasma samples without any ACE inhibitors and those obtained from the patients taking 20 mg enalapril, i.e., an ACE inhibitor (Column 3, Lines 5-25). ACE activity was also measured by established methods and ACE activity in absence and presence of ACE inhibitors was evaluated on the basis of a standard curve (Column 4, Lines 8 to 53). The inhibition of ACE activity was measured with samples taken at different time intervals post ingestion of enalapril. Thus, Brunner et al. inherently teach measuring ACE activity in a human body fluid, i.e., plasma, wherein measurement is taken on the samples at a first time and a second time, wherein said second measurement is at a time interval after the first measurement. As the ACE activity is measured in more than one plasma samples and in samples obtained before and after ingestion of enalapril, Brunner et al. teach determination of a drug in a human body fluid sample (i.e., plasma), wherein said drug is an ACE inhibitor. Furthermore, Brenner et al. compare the measured ACE activity in plasma samples taken before and after ingestion of enalapril and compare those activities with a base line and a standard curve for the ACE activity (Column 4, Lines 8 to 53 and Table 1).

Therefore, the reference anticipates the claims.

Claim Rejections - 35 U.S.C. § 103

14. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § *102*(f) or (g) prior art under 35 U.S.C.§ 103(a).

16. Claims 1-10, and 12-24 are rejected under 35 U.S.C. § 103 (a) as obvious over Yoshikawa et al. (U.S. Patent 5,369,015) in view of Brunner et al. (U.S. Patent 5,407,803) and further in view of Ryan et al. (US 4,335,041).

Teachings from each of Yoshikawa et al., and Brunner et al. have been discussed *supra.*

Yoshikawa et al., however, do not teach a method to evaluate ACE activity via measuring the optical density of the reaction mixture. They also do not teach that the fluid wherein enzyme activity/inhibitor was evaluated is a body fluid (i.e., urine) or the drug that inhibits enzyme activity is enalapril.

Brunner et al. teach determining a drug in a human body sample, wherein said drug is an ACE inhibitor. Furthermore, Brunner et al. compare the measured ACE activity in plasma samples taken before and after ingestion of enalapril and compare those activities with a base line and a standard curve for the ACE activity (Column 4, Lines 8 to 53 and Table 1).

Ryan et al. teach the functional equivalence of assaying ACE in urine or serum in the presence of dialyzable ACE inhibitors (column 6, lines 36-44) with increased sensitivity than previously known methods (Column 5, Lines 37-45; Column 6, Lines 45-52). Ryan et al's method enable evaluation of ACE activity in not only serum but other clinical samples (e.g., urine, tissue and tissue culture cells).

One having ordinary skill in the art at the time that said invention was made, would have been motivated to modify Yoshikawa et al's teachings according to the teachings from Brunner et al. and Ryan et al. to obtain a method to determine a drug in a fluid sample, wherein, drug is an ACE inhibitor and fluid sample is urine, and in said method the ACE activity in absence and presence of an inhibitor is measured (i) on a given ACE substrate via measuring optical density of the reaction mixtures with and without said drug, i.e., inhibitor compound, and (ii) comparing the data on optical density measurements with a standard curve. This is because, Yoshikawa et al., Brunner et al. and Ryan et al. teach measuring ACE activity inhibition on a given substrate in the absence and presence of an inhibitor compound (i.e., a drug). Said inhibition is quantified by comparing data on ACE activity measured as optical density with a standard curve in more than two fluid samples. Said activity is evaluated via measuring the optical density of said reaction mixtures containing ACE, test compound and ACE substrate. Brunner et al. remedy the deficiency in the teachings from Yoshikawa et al. because Brenner et al. determine a drug in a human body sample, i.e., plasma, wherein said drug is an ACE inhibitor. Brenner et al also compare the measured ACE activity in plasma samples taken before and after ingestion of enalapril and compare those activities with a base line and a standard curve for the ACE activity. Enalapril is a known ACE inhibitor drug. Ryan et al. remedy the deficiency of determining the ACE inhibitor/drug in a urine sample in teachings from Yoshikawa et al. because Ryan et al.

teach the functional equivalence of assaying ACE activity in urine or serum samples in the presence or absence of ACE inhibitors.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify Yoshikawa et al's teachings according to the teachings from Brunner et al. and Ryan et al., because all of the cited prior art references teach determining ACE activity in presence and absence of an ACE inhibitor, wherein said ACE inhibitor is a drug. Brunner et al. remedy the deficiency in teachings from Yoshikawa et al. of determining a drug in a human body sample, wherein said drug is an ACE inhibitor. Furthermore, Brunner et al. compare the measured ACE activity in plasma samples taken before and after ingestion of enalapril and compare those activities with a base line and a standard curve for the ACE activity in Yoshikawa et al's teachings. Ryan et al. remedy the deficiency of evaluating an ACE inhibitor/ACE drug in a urine sample because they teach the functional equivalence of assaying ACE/ACE inhibitor in a clinical sample, wherein said sample is urine, serum, tissue or cultured cell.

None of the above discussed prior art references teach the exact same assay conditions or concentrations of reaction mixture components to determine the presence of a drug in a fluid sample. However, the adjustment of particular conventional working conditions (e.g., the quantities of each one of components in reaction mixture) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter that is well within the purview of the skilled artisan.

From the teachings of the cited references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

17. No Claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571)-272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Daylight Saving, or Standard time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (571)-272-0926. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9306.

Kailash C. Srivastava, Ph.D.
Patent Examiner
Art Unit 1651
(571)-272-0923

April 14, 2004

Jon P. Weber, Ph.D
Primary Examiner